

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLULAVAL safely and effectively. See full prescribing information for FLULAVAL.

FLULAVAL™ (Influenza Virus Vaccine)

Intramuscular Injection

2006-2007 Formula

Initial US Approval: 2006

INDICATIONS AND USAGE

- FLULAVAL is an influenza virus vaccine indicated for active immunization of adults 18 years of age and older against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine. (1)
- This indication is based on immune response elicited by FLULAVAL, and there have been no controlled trials demonstrating a decrease in influenza disease after vaccination with FLULAVAL. (14)
- FLULAVAL is not indicated for use in children. (8.4)

DOSAGE AND ADMINISTRATION

- A single 0.5-mL intramuscular injection. (2.2)

DOSAGE FORMS AND STRENGTHS

- 5-mL multi-dose vial containing 10 doses (each dose is 0.5 mL). (3)
- Each 0.5-mL dose contains 15 micrograms (mcg) of influenza virus hemagglutinin (HA) of each of the following 3 strains: A/New Caledonia/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004. (3, 11)
- Thimerosal, a mercury derivative, is added as a preservative. Each 0.5 mL dose contains 25 mcg mercury. (11)

CONTRAINDICATIONS

- Known systemic hypersensitivity reactions to egg proteins, or any other component of FLULAVAL. (4.1)
- Life threatening reaction to previous influenza vaccination. (4.1)
- Delay immunization in a patient with an acute evolving, neurologic disorder. (4.2)

WARNINGS AND PRECAUTIONS

- If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLULAVAL should be based on careful consideration of the potential benefits and risks. (5.1)

- Individuals with bleeding disorders or receiving anticoagulants are at risk of hematoma formation following intramuscular administration. Take steps to control the risk of hematoma following the injection in these persons. (5.2)
- Immunocompromised persons may have a reduced immune response to FLULAVAL. (5.3)

ADVERSE REACTIONS

- Most common ($\geq 10\%$) local adverse events were pain, redness, and/or swelling at the injection site. (6.2)
- Most common ($\geq 10\%$) systemic adverse events were headache, fatigue, myalgia, low grade fever, and malaise. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or VAERS at 1-800-822-7967 and www.vaers.hhs.gov.

DRUG INTERACTIONS

- Do not mix with any other vaccine in the same syringe or vial. (7.1)
- May increase blood levels of warfarin, theophylline, and phenytoin. (7.2)
- Immunosuppressive therapies may reduce immune responses to FLULAVAL. (7.3)

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of FLULAVAL have not been established in pregnant women and children. (8.1, 8.4)
- Antibody responses were lower in geriatric subjects than in younger subjects. (8.5)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLULAVAL is indicated for active immunization of adults (18 years of age and older) against influenza disease caused by influenza virus subtypes A and type B contained in the vaccine (see DOSAGE FORMS AND STRENGTHS [3]).

This indication is based on immune response elicited by FLULAVAL, and there have been no controlled trials demonstrating a decrease in influenza disease after vaccination with FLULAVAL (see CLINICAL STUDIES [14]).

FLULAVAL is not indicated for use in children.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

Inspect FLULAVAL visually for particulate matter and/or discoloration prior to administration whenever solution and container permit. If either of these conditions exists, the vaccine should not be administered.

Shake the multi-dose vial vigorously each time before withdrawing a dose of vaccine.

Between uses, return the multi-dose vial to the recommended storage conditions, between 2° and 8°C (36° and 46°F). **Do not freeze.** Discard if the vaccine has been frozen. Once entered, a multi-dose vial, and any residual contents, should be discarded after 28 days.

A separate sterile syringe and needle or a sterile disposable unit should be used for each injection to prevent transmission of infectious agents from one person to another. Needles should be disposed of properly and should not be recapped.

2.2 Recommended Dose and Schedule

FLULAVAL should be administered as a single 0.5-mL injection by the intramuscular route preferably in the region of the deltoid muscle of the upper arm.

The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. A needle length of ≥ 1 inch is preferred because needles < 1 inch might be of insufficient length to penetrate muscle tissue in certain adults. Before injection, the skin over the site to be injected should be cleansed with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Do not inject intravenously or subcutaneously.

3 DOSAGE FORMS AND STRENGTHS

FLULAVAL is available as 5-mL multi-dose vials containing 10 doses. Each 0.5-mL dose contains a total of 45 mcg hemagglutinin from the 3 influenza virus types in the vaccine.

4 CONTRAINDICATIONS

4.1 Hypersensitivity

FLULAVAL should not be administered to anyone with known systemic hypersensitivity reactions to egg proteins (eggs or egg products), to chicken proteins, or to any component of FLULAVAL, or who has had a life threatening reaction to previous influenza vaccination.

4.2 Acute Neurologic Disorder

Immunization should be delayed in a patient with an acute evolving neurologic disorder but should be considered when the disease process has been stabilized.

5 WARNINGS AND PRECAUTIONS

5.1 Guillain-Barré Syndrome

If Guillain-Barré syndrome has occurred within 6 weeks of receipt of prior influenza vaccine, the decision to give FLULAVAL should be based on careful consideration of the potential benefits and risks.

5.2 Persons at Risk of Bleeding

FLULAVAL should not be given to individuals with bleeding disorders such as hemophilia or thrombocytopenia, or to persons on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration. If the decision is made to administer FLULAVAL to such persons, steps should be considered to control the risk of hematoma following the injection.

5.3 Altered Immunocompetence

If FLULAVAL is administered to immunocompromised persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.

5.4 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the patient's immunization history for possible vaccine sensitivity, previous vaccination-related adverse reactions and occurrence of any adverse event-related symptoms and/or signs, in order to determine the

existence of any contraindication to immunization with FLULAVAL and to allow an assessment of benefits and risks. Epinephrine injection (1:1,000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

5.5 Limitations of Vaccine Effectiveness

Vaccination with FLULAVAL may not protect 100% of susceptible individuals.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

Adverse event information from clinical trials provides a basis for identifying adverse events that appear to be related to vaccine use and for approximating rates. However, because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine, and may not reflect the rates observed in practice.

Safety information for FLULAVAL was collected in 2 clinical trials and is discussed in the following section (6.2). There is the possibility that broad use of FLULAVAL could reveal adverse events not observed in clinical trials.

6.2 Clinical Trials Experience

Safety information for FLULAVAL was collected in 2 randomized, controlled clinical trials, one in the United States (IDB707-105) and the second in Canada (SPD707-104). The safety population from these trials includes 1,049 adults 18 years of age and older vaccinated with products representative of the current formulation of FLULAVAL. The US study included subjects 18 to 64 years of age who were randomized to receive FLULAVAL (n = 721) or a US-licensed trivalent, inactivated influenza virus vaccine (FLUZONE) (n = 279). The Canadian study compared 4 vaccine groups: FLULAVAL, a similar investigational formulation of FLULAVAL with reduced thimerosal, and 2 Canadian-licensed trivalent influenza vaccines.

Among recipients of FLULAVAL, 56.6% were women; 92.4% of subjects were White, 6.5% Black, 2.7% Native American, and 1.0% Asian. In the US study, 74.8% of the recipients of FLULAVAL were Hispanic/Latino. The mean age of subjects in the US study was 38 years (range 18-64 years) and 19% of subjects were 50 to 64 years of age. In the Canadian study, the mean age was 63 years (range 50-92 years), and 46.6% were 65 years of age and older.

A series of symptoms and/or findings were specifically solicited by a diary/memory aid used by subjects for at least the day of vaccination and 3 days post-treatment (see Table 1). Subjects were actively queried about changes in their health status through 42 days post-vaccination in the US trial, and six months post-vaccination in the Canadian study. In addition, spontaneous reports of adverse events were also collected (see Table 2).

Table 1. Solicited Adverse Events in the First 4 Days After Administration of FLULAVAL or Comparator Influenza Vaccine

	US Trial Adults 18 to 64 years of age (80% <50 years of age)		Canadian Trial Adults 50 years of age and older
	FLULAVAL N = 721	Comparator Influenza Vaccine* N = 279	FLULAVAL† N = 328
Local Adverse Events			
Pain	174 (24%)	85 (31%)	70 (21%)
Redness	76 (11%)	28 (10%)	48 (14%)
Swelling	71 (10%)	29 (10%)	21 (6%)
Systemic Adverse Events			
Headache	127 (18%)	48 (17%)	34 (10%)
Fatigue	123 (17%)	43 (15%)	33 (10%)
Myalgia	93 (13%)	44 (16%)	35 (11%)
Fever‡	79 (11%)	28 (10%)	1 (1%)
Malaise	73 (10%)	28 (10%)	13 (4%)
Sore throat	64 (9%)	26 (9%)	17 (5%)
Reddened eyes	44 (6%)	15 (5%)	10 (3%)
Cough	44 (6%)	19 (7%)	11 (3%)
Chills	38 (5%)	6 (2%)	10 (3%)
Chest tightness	24 (3%)	4 (1%)	6 (2%)
Facial swelling	7 (1%)	1 (1%)	1 (1%)

Results >1% reported to nearest whole percent; results >0 but ≤1 reported as 1%.

* US-licensed trivalent, inactivated influenza virus vaccine (FLUZONE).

† Includes subjects who received FLULAVAL and a similar investigational formulation of FLULAVAL with reduced thimerosal.

‡ Fever defined as ≥37.5°C in the US study, and ≥38.0°C in the Canadian study.

Local adverse events occurred with similar frequency in the 2 trials. In the US study, the only significant difference between FLULAVAL and a US-licensed trivalent, inactivated influenza virus vaccine was an increased frequency of chills in subjects receiving FLULAVAL.

Table 2 summarizes the most common adverse events in the 2 clinical trials; adverse events were reported, either spontaneously or in response to queries about changes in health status. The most common events were headache and cough in both studies. These, as well as throat pain, were the only adverse events reported by >1% of subjects in the US trial. The Canadian trial featured a longer safety follow-up (6 months vs. 42 days) and enrolled a population exclusively 50 years of age and older. Therefore, spontaneous adverse event reports were more frequent in this trial. As indicated in Table 2, upper respiratory infection, arthralgia,

myalgia, nasopharyngitis, back pain, injection site erythema, diarrhea, fatigue, nausea, and nasal congestion were each reported by $\geq 5\%$ of the recipients of FLULAVAL in the Canadian study.

Table 2. Adverse Events Reported Spontaneously* by $\geq 5\%$ of Subjects in Either Clinical Trial of FLULAVAL

	US Trial (safety follow-up 42 days) Adults 18 to 64 years of age (80% <50 years of age)		Canadian Trial (safety follow-up 6 months) Adults 50 years of age and older
	FLULAVAL N = 721	Comparator Influenza Vaccine [†] N = 279	FLULAVAL [‡] N = 328
Adverse Events			
Headache	49 (7%)	18 (7%)	63 (19%)
Cough	16 (2%)	5 (2%)	48 (15%)
Pharyngolaryngeal pain	17 (2%)	9 (3%)	38 (12%)
Upper respiratory infection	3 (1%)	2 (1%)	30 (9%)
Arthralgia	5 (1%)	3 (1%)	27 (8%)
Myalgia	4 (1%)	2 (1%)	23 (7%)
Nasopharyngitis	1 (1%)	1 (1%)	23 (7%)
Back pain	5 (1%)	3 (1%)	19 (6%)
Injection site erythema	2 (1%)	1 (1%)	18 (5%)
Diarrhea	5 (1%)	0	18 (5%)
Fatigue	6 (1%)	2 (1%)	17 (5%)
Nausea	5 (1%)	1 (1%)	17 (5%)
Nasal congestion	7 (1%)	2 (1%)	16 (5%)

Results $>1\%$ reported to nearest whole percent; results >0 but ≤ 1 reported as 1%.

* Adverse events in this table were reported spontaneously or in response to queries about changes in health status.

[†] US-licensed trivalent, inactivated influenza virus vaccine (FLUZONE).

[‡] Includes subjects who received FLULAVAL and a similar investigational formulation of FLULAVAL with reduced thimerosal.

6.3 Postmarketing Experience

The following additional adverse events have been identified during postapproval use of FLULAVAL in Canada since 2001. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their incidence rate or establish a causal relationship to vaccine exposure. Adverse events described here are included

because: a) they represent reactions which are known to occur following immunizations generally or influenza immunizations specifically; b) they are potentially serious; or c) the frequency of reporting.

Blood and lymphatic system disorders: Lymphadenopathy.

Eye disorders: Conjunctivitis, eye pain, photophobia.

Gastrointestinal disorders: Dysphagia, vomiting.

General disorders and administration site conditions: Chest pain, injection site inflammation, rigors, asthenia, injection site rash, influenza-like symptoms, abnormal gait, injection site bruising, injection site sterile abscess.

Immune system disorders: Allergic edema of the face, allergic edema of the mouth, anaphylaxis, allergic edema of the throat.

Infections and infestations: Pharyngitis, rhinitis, laryngitis, cellulitis.

Musculoskeletal and connective tissue disorders: Muscle weakness, back pain, arthritis.

Nervous system disorders: Dizziness, paresthesia, hypoesthesia, hypokinesia, tremor, somnolence, syncope, Guillain-Barré syndrome, convulsions/seizures, facial or cranial nerve paralysis, encephalopathy, limb paralysis.

Psychiatric disorders: Insomnia.

Respiratory, thoracic, and mediastinal disorders: Dyspnea, dysphonia, bronchospasm, throat tightness.

Skin and subcutaneous tissue disorders: Urticaria, localized or generalized rash, pruritus, periorbital edema, sweating.

Vascular disorders: Flushing, pallor.

6.4 Adverse Events Associated with Influenza Vaccines

Anaphylaxis has been reported after administration of FLULAVAL. Although FLULAVAL contains only a limited quantity of egg protein, this protein can induce immediate hypersensitivity reactions among persons who have severe egg allergy. Allergic reactions include hives, angioedema, allergic asthma, and systemic anaphylaxis (see CONTRAINDICATIONS [4]).

The 1976 swine influenza vaccine was associated with an increased frequency of Guillain-Barré syndrome (GBS). Evidence for a causal relation of GBS with subsequent vaccines prepared from other influenza viruses is unclear. If influenza vaccine does pose a risk, it is probably slightly more than 1 additional case/1 million persons vaccinated.

Neurological disorders temporally associated with influenza vaccination such as encephalopathy, optic neuritis/neuropathy, partial facial paralysis, and brachial plexus neuropathy have been reported.

Microscopic polyangitis (vasculitis) has been reported temporally associated with influenza vaccination.

7 DRUG INTERACTIONS

7.1 Concomitant Administration with Other Vaccines

There are no data to assess the concomitant administration of FLULAVAL with other vaccines. If FLULAVAL is to be given at the same time as another injectable vaccine(s), the vaccines should always be administered at different injection sites. FLULAVAL should not be mixed with any other vaccine in the same syringe or vial.

7.2 Warfarin, Theophylline, and Phenytoin

Although it has been reported that influenza vaccination may inhibit the clearance of warfarin, theophylline, and phenytoin, controlled studies have yielded inconsistent results regarding pharmacokinetic interactions between influenza vaccine and these medications. Nevertheless, clinicians should consider the potential for an interaction when FLULAVAL is administered to persons receiving these drugs.

7.3 Immunosuppressive Therapies

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs, and corticosteroids (used in greater than physiologic doses), may reduce the immune response to FLULAVAL.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with FLULAVAL. It is also not known whether FLULAVAL can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. FLULAVAL should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether FLULAVAL is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FLULAVAL is administered to a nursing woman.

8.4 Pediatric Use

Safety and effectiveness of FLULAVAL in pediatric patients have not been established.

8.5 Geriatric Use

In the 2 clinical trials, there were 157 subjects who were ≥ 65 years of age and received FLULAVAL; 21 of these subjects were ≥ 75 years of age. Hemagglutination-inhibiting (HI) antibody responses were lower in geriatric subjects than younger subjects after administration of FLULAVAL. Solicited adverse events were similar in frequency to those reported in younger subjects (see ADVERSE REACTIONS [6]).

11 DESCRIPTION

FLULAVAL is a trivalent, split-virion influenza virus vaccine prepared from virus propagated in the allantoic cavity of embryonated hens' eggs. Each of the influenza virus strains is produced and purified separately. The virus is inactivated with ultraviolet light treatment

followed by formaldehyde treatment, purified by centrifugation, and disrupted with sodium deoxycholate.

FLULAVAL is a homogenized, sterile, colorless to slightly opalescent suspension in a phosphate-buffered saline solution. FLULAVAL has been standardized according to USPHS requirements for the 2006–2007 influenza season and is formulated to contain 45 micrograms (mcg) hemagglutinin per 0.5-mL dose in the recommended ratio of 15 mcg HA of each of the following 3 strains: A/New Caledonia/20/99 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004. Thimerosal, a mercury derivative, is added as a preservative. Each dose contains 25 mcg mercury. Each dose may also contain residual amounts of egg proteins (≤ 1 mcg ovalbumin), formaldehyde (≤ 25 mcg), and sodium deoxycholate (≤ 50 mcg). Antibiotics are not used in the manufacture of this vaccine.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Influenza illness and its complications follow infection with influenza viruses. Global surveillance of influenza identifies yearly antigenic variants. For example, since 1977, antigenic variants of influenza A (H1N1 and H3N2) viruses and influenza B viruses have been in global circulation. Specific levels of HI antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the antibody titers have been used as a measure of vaccine activity. In some human challenge studies, antibody titers of $\geq 1:40$ have been associated with protection from influenza illness in up to 50% of subjects.^{1,2} Antibody against one influenza virus type or subtype confers little or no protection against another virus. Furthermore, antibody to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Frequent development of antigenic variants through antigenic drift is the virological basis for seasonal epidemics and the reason for the usual change of one or more new strains in each year's influenza vaccine. Therefore, inactivated influenza vaccines are standardized to contain the hemagglutinins of strains (i.e., typically 2 type A and 1 type B), representing the influenza viruses likely to circulate in the United States in the upcoming winter.

Annual revaccination with the current vaccine is recommended because immunity declines during the year after vaccination, and because circulating strains of influenza virus change from year to year.³

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

FLULAVAL has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

14 CLINICAL STUDIES

In 2 randomized, active-controlled trials of FLULAVAL, the immune responses, specifically HI antibody titers to each virus strain in the vaccine, were evaluated in sera obtained

21 days after administration of FLULAVAL. No controlled trials demonstrating a decrease in influenza disease after vaccination with FLULAVAL have been performed.

A 1,000-subject randomized, blinded, and controlled study was performed in the United States in 18- to 64-year-old healthy adults. A total of 721 subjects received FLULAVAL, and 279 received a US-licensed trivalent, inactivated influenza virus vaccine (FLUZONE); 959 subjects had complete serological data and no major protocol deviations. Among recipients of FLULAVAL, 57.4% were women. The mean age of recipients of FLULAVAL was 37.9 years; 80.4% were 18 to 49 years of age and 19.6% were 50 to 64 years of age.

A second, randomized, blinded, and controlled study which enrolled 658 subjects 50 years of age and older (stratified by age <65 and ≥65 years) was conducted in Canada. This study included elderly persons with medically controlled chronic high-risk diagnoses who were clinically stable. This study compared 4 vaccine groups: FLULAVAL, a similar investigational formulation of FLULAVAL with reduced thimerosal, and 2 Canadian-licensed trivalent influenza vaccines. Results from the 2 groups that received FLULAVAL were submitted in support of the US licensure of FLULAVAL. Among these 2 groups, 54.9% of subjects were women. The mean age of recipients of FLULAVAL was 63 years; 53.4% were 50 to 64 years of age and 46.6% were 65 years of age and older.

For both studies, analysis of the following co-primary endpoints were performed for each HA antigen contained in the vaccine: 1) assessment of the lower bounds of 2-sided 95% confidence intervals for the proportion of subjects with HI antibody titers of ≥1:40 after vaccination, and 2) assessment of the lower bounds of 2-sided 95% confidence intervals for rates of seroconversion (defined as a 4-fold increase in post-vaccination HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40). The pre-specified targets for the 2 endpoints varied by study because of age of subjects enrolled. The pre-specified target for endpoint 1) was 70% in the US study and 60% in the Canadian study. For endpoint 2) the pre-specified target was 40% in the US study and 30% in the Canadian study. For the Canadian study, the primary endpoints, as originally designed, were descriptive comparisons of immune response; therefore, a post-hoc analysis of the endpoints, as described above, was performed.

Table 3. Serum Hemagglutination-Inhibiting (HI) Antibody Responses to FLULAVAL in 2 Clinical Trials* (Per Protocol cohort)[†]

US Trial in Adults 18 to 64 years of age	% of Subjects (lower bound of 2-sided 95% confidence interval) [‡]		
	FLULAVAL N = 692		Primary endpoint met post-vaccination
HI titers ≥40 against:	Pre-vaccination	Post-vaccination	
A/New Caledonia/20/99 (H1N1)	24.6	96.5 (94.9)	Yes
A/Wyoming/03/03 (H3N2)	58.7	98.7 (97.6)	Yes
B/Jiangsu/10/03	5.4	62.9 (59.1)	No
Seroconversion [§] to:			
A/New Caledonia/20/99 (H1N1)	85.6 (82.7)		Yes
A/Wyoming/03/03 (H3N2)	79.3 (76.1)		Yes
B/Jiangsu/10/03	58.4 (54.6)		Yes
Canadian Trial in Adults ≥50 years of age	% of Subjects (lower bound of 2-sided 95% confidence interval) [‡]		
	FLULAVAL N = 324		Primary endpoint met post-vaccination
HI titers ≥40 against:	Pre-vaccination	Post-vaccination	
A/New Caledonia/20/99 (H1N1)	39.5	86.4 (82.2)	Yes
A/Wyoming/03/03 (H3N2)	67.9	99.1 (97.3)	Yes
B/Jiangsu/10/03	10.2	57.1 (51.5)	No
Seroconversion [§] to:			
A/New Caledonia/20/99 (H1N1)	44.8 (39.3)		Yes
A/Wyoming/03/03 (H3N2)	69.1 (63.8)		Yes
B/Jiangsu/10/03	49.1 (43.5)		Yes

* Results obtained following vaccination with FLULAVAL manufactured for the 2004–2005 season.

[†] Per Protocol cohort for immunogenicity included subjects with complete pre- and post-dose HI titer data and no major protocol deviations.

[‡] Lower bounds were calculated using Clopper-Pearson method.

[§] Seroconversion = a 4-fold increase post-vaccination in HI antibody titer from pre-vaccination titer ≥1:10, or an increase in titer from <1:10 to ≥1:40.

^{||} Includes subjects who received FLULAVAL and a similar investigational formulation of FLULAVAL with reduced thimerosal.

Across both studies, serum HI antibody responses to FLULAVAL met the pre-specified seroconversion criteria for all 3 virus strains, and also the pre-specified criterion for the proportion of subjects with HI titers ≥1:40 for both influenza A viruses. In both trials, both FLULAVAL and the comparator vaccine did not meet the pre-specified criterion for the proportion of subjects with HI titers ≥1:40 for the influenza B virus. The clinical relevance of this

finding on vaccine-induced protection against illness caused by influenza type B strains is unknown.

15 REFERENCES

1. Hannoun C, Megas F, Piercy J. Immunogenicity and protective efficacy of influenza vaccination. *Virus Res* 2004;103:133-138.
2. Hobson D, Curry RL, Beare AS, et al. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg Camb* 1972;70:767-777.
3. Centers for Disease Control and Prevention. Prevention and control of influenza: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 2006;55(RR-10):1-42.

16 HOW SUPPLIED/STORAGE AND HANDLING

FLULAVAL is supplied in a 5-mL multi-dose vial containing ten 0.5-mL doses. Once entered, the multi-dose vial should be discarded after 28 days.

Store FLULAVAL refrigerated between 2° and 8°C (36° and 46°F). **Do not freeze.**

Discard if the vaccine has been frozen. Store in the original package to protect from light.

Do not use after expiration date shown on the label.

The vial stopper does not contain latex.

NDC 19515-883-07 (package of 1 vial containing 10 doses)

17 PATIENT COUNSELING INFORMATION

Vaccine recipients and guardians should be informed by their healthcare provider of the potential benefits and risks of immunization with FLULAVAL. When educating vaccine recipients and guardians regarding potential side effects, clinicians should emphasize that (1) FLULAVAL contains non-infectious killed viruses and cannot cause influenza and (2) FLULAVAL is intended to provide protection against illness due to influenza viruses only, and cannot provide protection against all respiratory illness.

Vaccine recipients and guardians should be instructed to report any severe or unusual adverse reactions to their healthcare provider.

The vaccine recipient or guardian should be given the Vaccine Information Statements, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization. These materials are available free of charge at the CDC website (www.cdc.gov/nip).

Vaccine recipients and guardians should be instructed that annual revaccination is recommended.

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